In the Specification:

Please amend the specification as shown:

Please delete the paragraphs on page 14, lines 7-18 and replace them with the following amended paragraphs:

Figure 49 shows a protein motif used in the measurement of the activity of Caspase-3 (peptide disclosed as SEQ ID NO: 82).

Figure 50 shows a cross correlation with *in vitro* protease activity. Three types of tandem fluorescent protein samples obtained by insertion of the DEVD (SEQ ID NO: 82) sequence into a linker portion were prepared: ECFP-keima 616, keima 616-ECFP, and EGFP-mRFP1 (x 2). The upper case indicates autocorrelation and cross correlation functions obtained before addition of Caspase-3. The middle case indicates a cross correlation function obtained after addition of Caspase-3. The lower case indicates fluorescence intensity obtained after addition of Caspase-3.

Figure 51 shows a relative amplitude in each fusion protein motif (peptide disclosed as SEQ ID NO: 82).

Figure 52 shows detection of the cleavage of a peptide chain with Caspase-3 (SDS-PAGE) (peptide disclosed as SEQ ID NO: 82).

Please delete the paragraph on page 38, line 22 to page 39, line 7 and replace it with the following amended paragraph:

Example 4: Targeting to mitochondria

12 amino acids (MLSLRQSIRFFK) (SEQ ID NO: 83) at the N-terminus of cytochrome oxidase subunit 4 derived from yeast were added to each of the N-termini of KO and mKO. Thereafter, targeting to the mitochondria of HeLa cells was conducted, so as to label the mitochondria. As a result, it was confirmed that KO (dimer) was not exactly targeted to the mitochondria, and that the mitochondria was stained in a granulated state (Figure 4). On the other hand, mKO (monomer) was exactly targeted to the mitochondria, and narrow filamentous mitochondria were observed. Thus, effectiveness obtained by monomerization was confirmed (Figure 5).

Please delete the paragraph on page 50, lines 9-22 and replace it with the following amended paragraph:

At least one type of protein used to perform intramolecular FRET should be a monomer. (A) the combination of the monomer (white) with the dimer (black) (Figure 35A). The combination of the dimer (polymer) fluorescent protein MiCy with the monomer fluorescent protein mKO corresponds to such a pattern. For example, it is considered that the combination of the dimer (white) with the dimer (black) causes a range such as a polymer (Figure 35B). In the case of the monomer fluorescent protein mKO and the dimer fluorescent protein MiCy, since the fluorescence spectrum of MiCy and the absorption spectrum of mKO partially overlap, it is possible to measure FRET (fluorescence resonance energy transfer method) using both proteins (Figure 36). Thus, MiCy is ligated to mKO, using a linker that contained DEVD (Asp-Glu-Val-Asp) (SEQ ID NO: 82) as a Caspase-3 recognition sequence (the amino acid sequence thereof is

shown in SEQ ID NO: 35, and the nucleotide sequence thereof is shown in SEQ ID NO: 36). Thereafter, the cleavage of the linker sequence due to activation of Caspase-3 was measured by FRET.

Please delete the paragraph on page 50, line 24 to page 51, line 18 and replace it with the following amended paragraph:

MiCy, the linker, and mKO were ligated to one another in this order, and the obtained ligate was then subcloned into the BamH1-EcoR1 site of the *Escherichia coli* expression vector $pRSET_B$, so that it was allowed to express in *Escherichia coli* JM109 (DE3). The used linker had the following sequence: GGSGGDEVDGTGGS (Gly-Gly-Ser-Gly-Gly-Asp-Glu-Val-Asp-Gly-Thr-Gly-Gly-Ser) (SEQ ID NO: 84). This construct was referred to as MiCy-DEVD-mKO (SEQ ID NO: 82). The expressed recombinant fusion protein was purified with Ni-NTA agarose. The purified recombinant fusion protein was subjected to gel filtration using a sephadex G-25 column, and the buffer was substituted with a 150 mM KCl and 50 mM HEPES-KOH (pH 7.4) solution. For activity measurement, recombinant Active-Caspase-3 (MBL: BV-1083-9) was used. Each recombinant fusion protein was poured into a solution that contained 20 mM HEPES-KOH (pH7.4), 100 mM NaCl, 0.1% CHAPS, and 10% sucrose, resulting in a concentration of 1 mg/ml. Thereafter, 1 unit of the recombinant Active-Caspase-3 was added thereto, followed by reaction at 30°C for 3 hours. The fluorescence spectrum of the reaction solution was excited at 440 nm and measured before and after the reaction. For such measurement, a fluorospectrophotometer F-2500 (HITACHI) was used. As a

result, it was found that FRET took place and the fluorescence peak (559 nm) of mKO appeared before addition of Caspase-3, but that after the addition thereof, FRET disappeared due to the cleavage of the linker and the fluorescence peak (559 nm) of mKO thereby disappeared, so that only the fluorescence peak (495 nm) of MiCy remained (Figure 37).

Please delete the paragraph on page 51, lines 20-25 and replace it with the following amended paragraph:

MiCy-DEVD-mKO (SEQ ID NO: 82) was subcloned into the BamH1-EcoR1 site of the animal cell expression vector pCS2+. The thus prepared vector was introduced into HeLa-S3 cells, using Polyfect (QIAGEN). Twenty-four hours after introduction of the gene, the culture solution was substituted with an HBSS (Hanks' Balanced Salt Solution) that contained 500 ng/ml anti-Fas antibody (CH-11: MBL) and 10 μg/ml cycloheximide, so as to induce apoptosis, followed by the imaging of Caspase-3 activity measurement.

Please delete the paragraph on page 63, lines 5-10 and replace it with the following amended paragraph:

TCS SP2 SOBS (Leica) and the FCCS system were used for fluorescence cross-correlation measurement. For EGFP-(spacer) DEVD-mRFP1 (SEQ ID NO: 82), 458-nm Argon ion Laser and 594-nm HeNe Laser were used, and two wavelengths excitation was carried out. In addition, as the combination of ECFP with the keima 616 protein, 458-nm

Argon Laser was used. Further, as light receiving band-pass filters, the following filters were used: EGFP: 500-550; mRFP1: 607-683; ECFP: 470-500; and keima 616: 535-585.

Please delete the paragraph on page 63, lines 12-23 and replace it with the following amended paragraph:

The amino acid sequence DEVD (SEQ ID NO: 82) which is cleaved with Caspase-3 was introduced into the portion between EGFP and mRFP and also into the portion between keima 616 and ECFP (Figure 49). The recombinant EGFP-DEVD-mRFP1 (SEQ ID NO: 82) (x 2) (the amino acid sequence is shown in SEQ ID NO: 49, and the nucleotide sequence thereof is shown in SEQ ID NO: 50), ECFP-(spacer) DEVD-keima (SEQ ID NO: 82) 616 (the amino acid sequence is shown in SEQ ID NO: 51, and the nucleotide sequence thereof is shown in SEQ ID NO: 52), and keima 616-(spacer) DEVD-ECFP (SEQ ID NO: 82) (the amino acid sequence is shown in SEQ ID NO: 53, and the nucleotide sequence thereof is shown in SEQ ID NO: 54), were produced. Since the expressed proteins were constructed such that His-tag was attached to the N-terminus thereof, they were purified with Ni-agarose gel (QIAGEN). Purification was carried out in accordance with the protocols included therewith. Subsequently, these proteins were used to analyze cross-correlation.

Please delete the paragraph on page 63, line 24 to page 64, line 4 and replace it with the following paragraph:

For quantitative evaluation of cross-correlation, a value obtained by dividing the amplitude ($G_{cross}(0)$) of a cross-correlation function known as a relative amplitude by the

amplitude ($G_{lower}(0)$) of an autocorrelation function. In the case of EGFP-DEVD-mRFP1 (SEQ ID NO: 82) (x 2), the value of $G_{cross}(0)$ /$G_{lower}(0)$ was approximately 0.4 (Figure 51). A decrease in $G_{cross}(0)$ was observed as a result of addition of Caspase-3 (Figure 50).

Please delete the paragraph on page 64, lines 5-12 and replace it with the following paragraph:

In the case of the combination of ECFP with keima 616, the value of $G_{cross}(0)/G_{lower}(0)$ was 0.4 (Figure 51). A rapid decrease in $G_{cross}(0)$ was observed as a result of addition of Caspase-3. A decrease in $G_{cross}(0)$ indicates that fluorescence correlation disappeared as a result of addition of Caspase-3. In the case of the combined use of ECFP with keima 616, such correlation disappeared in a shorter time than in the case of EGFP-DEVD-mRFP (SEQ ID NO: 82). From these results, it became clear that the combined use of ECFP with keima 616 exhibits the interaction between proteins more easily and rapidly by the fluorescence cross-correlation method.

Please delete the paragraph on page 64, lines 14-19 and replace it with the following amended paragraph:

When keima 616-DEVD-ECFP (SEQ ID NO: 82) was reacted with Caspase-3, the bands with the sizes of keima 616 and ECFP could be confirmed. The presence of such proteins means that DEVD (SEQ ID NO: 82) was cleaved with Caspase-3 (Figure 52). In the case of Native-PAGE as well, two bands were confirmed after the reaction. The two

bands were identified to be keima 616 and ECFP, and thus it was found that the activity of Caspase-3 could be detected also by fluorescence detection (Figure 52).

Please insert the attached Sequence Listing in place of the Sequence Listing filed with the application.